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Pharmacology

Effect of Some Drugs and Medicinal Plants on Induced Hypertension in Rabbits

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Abstract **Original Research Article**

Introduction: The British hypertension society defines hypertension as existing when blood pressure is above 140/90. Similar threshold has been published by the European society of hypertension and the WHO. ***Aim of the study:*** To investigate the effect of certain drugs and medicinal plants on induced hypertension in rabbits. ***Methods:*** Hypertension was induced in them with (2 mg/kg hydrocortisone i.m. +2ml hypertonic saline (5%) orally) 2 times per day for three successive days until their blood pressure became >130/ 90 mmhg. Rabbits were divided into 7 groups. The first group is a control one while the rest are test groups for the following: atenolol, furosemide, candesartan, the aqueous extract of Hibiscus subdariffa, Plantago major, Teucrium polium. ***Results:*** According to ANOVA test: The most significantly effective drug in lowering both the systolic and diastolic blood pressure was furosemide followed by candesartan, atenolol and Hibiscus subdariffa respectively. Concerning the blood flow, candesartan was found to be the most significantly effective drug in increasing blood flow followed by furosemide and Hibiscus subdariffa respectively. Concerning the urine output furosemide was found to be the most significantly effective drug in increasing urine output followed by Hibiscus subdariffa. ***Conclusion:*** The aqueous extract of hibiscus subdariffa is effective as antihypertensive agent at the concentration mentioned. While aqueous extracts of plantago major and teucrium polium are not effective as antihypertensive drugs at the concentrations mentioned.

Keywords: Hibiscus subdariffa, plantago major, Teucrium polium, hypertension.

INTRODUCTION

The British hypertension society defines hypertension as existing when blood pressure is above 140/90. Similar threshold has been published by the European society of hypertension and the WHO-international society of hypertension.

Blood pressure Category	Systolic Bp mmHg	Diastolic Bp mmHg
Optimal	<120	<80
Normal	<130	<85
High normal	130-139	85-89
Hypertension		
Grade 1 (mild)	140-159	90-99
Grade 2 (moderate)	160-179	100-109
Grade 3 (severe)	>180	>110
Isolated systolic hypertension		
Grade 1	140-159	<90
Grade 2	>160	<90

The diagnosis of hypertension is therefore made when systolic and diastolic blood pressures values are above a specific threshold that corresponds to the level of Bp at which the cardiovascular complications and benefits of treatment outweigh the treatment costs and potential side effects of therapy.

Causes: Primary hypertension: unknown causes more than 90%

Causes of secondary hypertension: Alcohol, obesity, pregnancy, renal disease which may include parenchymal renal disease especially glomerulonephritis, renal vascular disease, polycystic kidney disease.

Endocrine disease: pheochromocytoma, cushing's syndrome, primary hyperaldosteronism, glucocorticoid suppressible hyperaldosteronism, hyperparathyroidism, acromegaly, primary hypothyroidism, thyrotoxicosis, congenital adrenal hyperplasia

MATERIALS AND METHODS

Animals

Eighty four healthy local domestic rabbits of male sex were used in this study, weighing (1000-1200 gm). They were supplied by the animal house of College of Medicine /Al-Nahrain University. These animals were kept in cages with a wire mesh in the floor. All the animals received oxoid pallet diet with water ad libitum. The animals were divided into two major groups.

Includes 42 rabbits. Hypertension was induced in them with (2 mg/kg hydrocortisone i.m. +2ml hypertonic saline (5%) orally) 2 times per day for three successive days until their blood pressure became >130/ 90 mmhg. All of the tested agents used in group one were applied to the animals at 9.00 A.M for 10 days. The animals were divided into 7 subgroups (each group contained 6 rabbits):

Subgroup A: treated with 2 ml/d of normal saline orally as a single dose as a control group.

Subgroup B: treated with 0.85 mg/kg/d of atenolol orally once daily as a treatment control.

Subgroup C: treated with 0.6 mg/kg/d of furosemide orally twice daily for 10 days as a treatment control.

Subgroup D: treated with 0.15 mg/kg/d of candesartan orally once daily for 10 days as test.

Subgroup E: treated with 0.5mg/kg/d of the aqueous extract of Hibiscus subdariffa orally once daily as a test.

Subgroup F: treated with 1mg/kg/d of the aqueous extract of Plantago major orally as test.

Subgroup G: treated with 50 mg/kg/d of the aqueous extract of Teucrium polium orally as a test.

The parameters were recorded once daily for each of the subgroups, and every hour for the duration of 8 hours for : Systolic blood pressure (SBp), Diastolic blood pressure (DBp), Heart rate. By microphone transducer. Urine output (collected by urethral catheter + graduated cylinder) measured per 8 hours. Blood flow (flow meter). By microphone transducer

The Tested Agents

Drugs		
Name	Manufacturer	Preparation
Atenolol(Vaseoten)	Medochemie Ltd,Limassol,Cyprus	tablets (each tablet contains 50 mg). crushed & dissolved in 58ml distilled water with shaking.
Hydrocortisone sodium succinate	Troge Medical GMBH,Hamburg Germany	(each vial contains 100mg).Dissolved in 100ml distilled water with shaking.
Candesartan cilexitel	AstraZeneca group of companies,aweeden	tablets (each tablet contains 16mg). crushed & dissolved in 106ml distilled water with shaking.
Furosemide	Holden Medical BV,Netherland	tablets (each tablet contains 40 mg). crushed & dissolved in 66ml distilled water with shaking.
Hypertonic saline 5%		prepared by the addition of 5 gm of Nacl to 100 ml of distilled water with shaking.
Phenylephrine hydrochloride	BDH chemicals Ltd,Poole England	(container contains 100 gm).Prepared by adding 20mg to 100ml distilled water to get the desired concentration 0.2mg/ml.
Pentobarbital sodium	Batch lab. Renaudine, France	vial contains 60mg/ml.
Extracts of medicinal plants		
Hibiscus subdariffa		The aqueous extract of the dried calices was used in this study in 0.5 mg/kg concentration
Plantago major		The aqueous extract of Plantago major leaves was used in this study in 1mg/kg concentration.
Teucrium polium		The aqueous extract of Teucrium polium flowers was used in this study in 50 mg/kg concentration

Aqueous extraction of the medicinal plants

Ten gram of the well grinded medicinal plant were taken and mixed to 100 ml of distilled water by the use of electric mixing machine for 15 minutes, and then the mixture was put in a hot plate magnetic stirrer for 48 hours in temperature of 45-50 ˚C continuously. Then the solution was put in centrifugation of 6000 RPM for 30 minutes, the sediment was discarded and the supernatant was taken, the procedure was repeated three times to ensure the discharge of sediment, then the supernatant was filtered by use of seitz filter (with pore diameter of 0.45 µm). The supernatant was collected in dark container [1].

METHODOLOGY

Anesthesia: For all of the procedures bellow, the animals have been anaesthetized with pentobarbital in a dose of 30 mg/kg i.p [2].

Induction of hypertension: By giving (2 mg/kg hydrocortisone i.m.+2ml hypertonic saline (5%) orally) 2 times per day for three successive days (until Bp becomes>130/90 mmHg) [3].

Blood pressure measuring (indirect method): Microphone transducer (4) applied on the medial aspect of the left thigh fixed to a constant tightness and connected to grass polygraph.

Heart Rate Measuring: The microphone transducer was used for the measurement of the peripheral pulse rate [4].

Measuring urine output: Urine output is collected to an accurate graduated cylinder by polythene catheter inserted into the urinary bladder. The first urine before treatment is voided out of cylinder [5].

Measuring blood flow: Fascias, muscles above the femoral artery are removed aside, and then a small arterial blood flow probe [6] is inserted carefully around the femoral artery.

Estimation of mean blood flow. Method of statistical analysis Student pooled t-test and ANOVA was used to estimate the significant difference between groups at ($P < 0.05$). SPSS program was used for that purpose.

RESULTS

The effect of the tested agents on the systolic and diastolic blood pressure, heart rate, blood flow and urine output for group one is presented in figures (1-5). The group contained 42 rabbits rendered hypertensive with 2mg/kg hydrocortisone i.m. +2ml hypertonic saline orally 2 times per day for 3 successive days until their blood pressure became more than 130/ 90mmhg. In group one the control group contained Hypertensive rabbits induced with hydrocortisone and hypertonic saline and treated with normal saline 2ml orally once daily for 10 days. For all of the agents used in group one, the treatment was applied to the animals at 9.00 a.m., orally, daily for ten days.

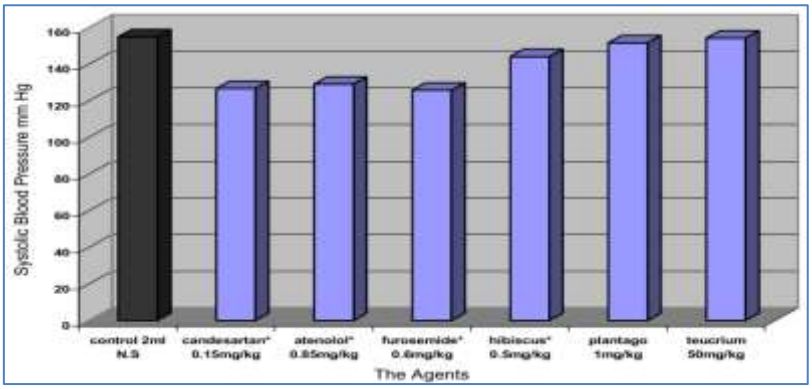

Fig-1: Effect of the studied agents on systolic blood pressure as compared with control

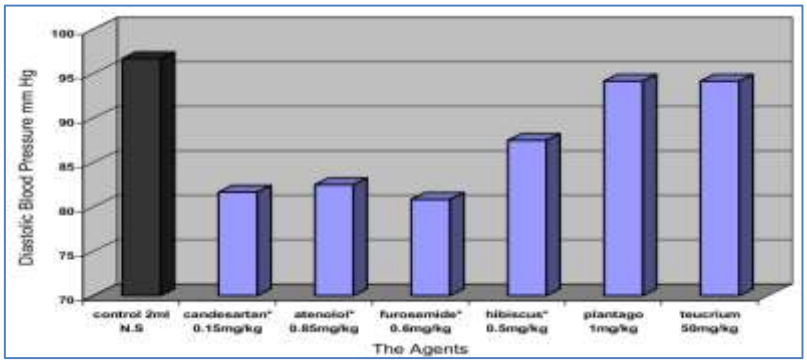

Fig-2: Effect of the studied agents on diastolic blood pressure as compared with control

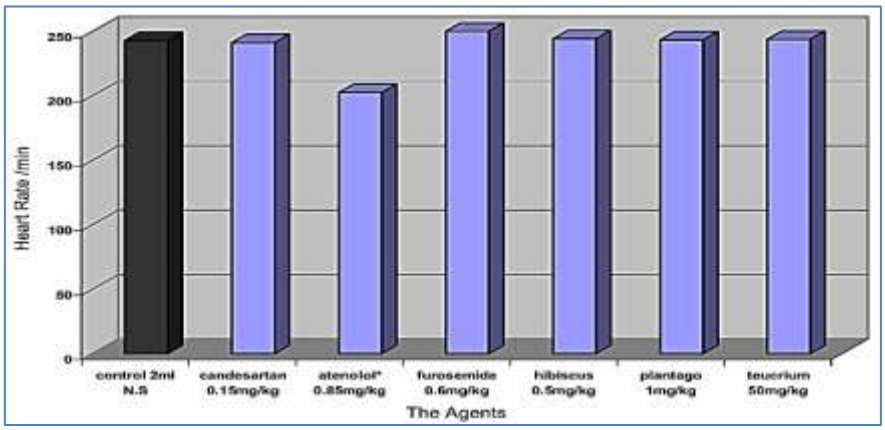

Fig-3: Effect of the studied agents on heart rate as compared with control

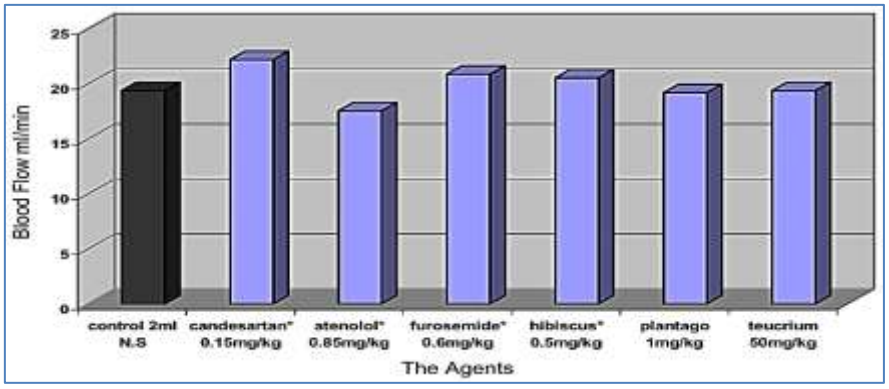

Fig-4: Effect of the studied agents on blood flow as compared with control

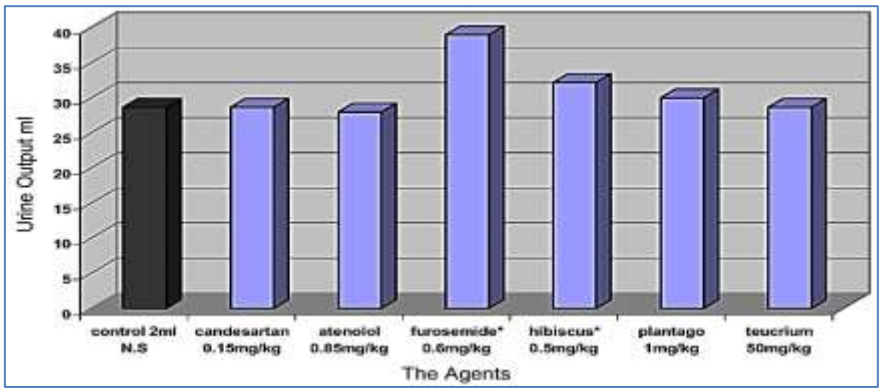

Fig-5: Effect of the studied agents on urine output as compared with control

DISCUSSION

In the present study, model of hypertension have been induced in the rabbits: done by hydrocortisone and hypertonic saline injection (3) in order to be in closer condition to that of essential hypertension, or in other words, as it has been explained in the review of literatures " so called volume loading hypertension" [6].

It is important to mention that the normal rabbit blood pressure is about 104±4/78±3 (4). Normal heart rate is about 246 beat /min. (2). Normal urine output is 112ml/day. Also, we should notice that there are biologic variations between these animals.

The method of induction (hypertension induced by hydrocortisone and hypertonic saline) was implicated with two important mechanisms:

1. Retention of sodium and water (as a result of the effect of hydrocortisone and injection of hypertonic saline. 2. Increase in the peripheral vascular resistance, which was the second stage of the volume loading hypertension.

Furosemide is a potent loop diuretic that is mostly effective on such hemodynamic disturbances. All diuretics initially lower the blood pressure by increasing urinary sodium excretion and/or reducing

plasma volume, extracellular fluid volume, and cardiac output. After that, the lowered plasma, extracellular fluid volume, and cardiac output return to normal. At this point and beyond, the lowered blood pressure is related to a decline in total peripheral resistance, thereby improving the underlying hemodynamic defect of hypertension. The mechanism which is responsible for the lowered peripheral resistance may involve decreased sensitivity of blood vessels to sodium or potassium channel activation [7]. After ten days of daily treatment, furosemide was found to be significantly effective in lowering both systolic and diastolic blood pressure by 30 and 16mmhg respectively, from that of the control. It was also significantly effective in increasing blood flow (this effect is related to the decrease in the peripheral vascular resistance due to vasodilation, which is the ultimate consequence of diuretic action). Urine output was also significantly increased, but there was no significant effect on heart rate.

Atenolol is a B1-selective antagonist that is devoid of intrinsic sympathomimetic activity. [8]. As a B- blocker, it has a negative inotropic and chronotropic effects. Atenolol mainly decreases blood pressure through reducing cardiac output (due to the decrease in the heart rate and contractility), and rennin release (B1-receptor blocking activity) [9].

The present study showed that candesartan was significantly effective in lowering both systolic and diastolic blood pressure by 29mmHg and 15 mmHg respectively, from that of the control.

Candesartan was also effective in increasing blood flow. This effect is due to the fact that candesartan is an angiotensin receptor blocker so that candesartan can block the vasoconstrictor and aldosterone secreting effects of angiotensin II by blocking the binding of angiotensin II to the AT1 receptors in many tissues such as smooth muscle and adrenal gland. Its action is therefore is independent of angiotensin II synthesis. The results of [10] on humans showed a decrease by 21 mmHg for systolic blood pressure and 13mmHg for diastolic blood pressure.

Candesartan was also significantly effective in increasing the blood flow. Hibiscus subdariffa was found to be significantly effective in lowering both systolic and diastolic blood pressure by 11 and 9mmhg respectively, from that of the control.

Hibiscus subdariffa was also significantly effective in increasing the urine output and blood flow. The significant decrease in both systolic and diastolic blood pressure and the increase in the blood flow can be explained by vasodilatation, this will lead to decrease in the peripheral vascular resistance, and lowering the blood pressure.

This vasodilatory effect may be due to the fact that Hibiscus subdariffa calices contain flavonoids in its chemical structure [11].

The Flavinoids of Hibiscus subdariffa has been reported to have a vasodilatory effect [12]. This will lead to decrease the peripheral vascular resistance and considered as one mechanism that can decrease the blood pressure.

In a study of [13] a hydroalcoholic extract of Hibiscus subdariffa showed in vitro an appreciable enzyme inhibiting activity towards angiotensin I converting enzyme (ACE) attributable to flavinoids. The significant increase in the urine output is another mechanism that can be employed in lowering blood pressure through diuresis and reducing the blood volume and cardiac output [14]. The diuretic effect may be due to flavonoids, anthocyanin, and the glycoside hibiscin.

Anthocyanin and the glycoside hibiscin were reported to have diuretic properties. Also the flavonoids were reported to have diuretic properties especially gossypetin [15].

The diuretic effect might be partly due to the vasodilatory effect; by increasing blood flow to the kidneys [15]. Another probable mechanism of the antihypertensive effect of Hibiscus subdariffa it could be mediated through acetylcholine-like and histamine-like mechanisms as well as via direct vaso-relaxant effects [1]. Regarding the hypotensive effect of Hibiscus subdariffa in our study it coincides with that described by [18]; their study showed a 11.2% and 10.7% decrease in both systolic and diastolic blood pressure respectively, while in our study the results showed 7% and 10% decrease in both systolic and diastolic blood pressure respectively.

Concerning the diuretic effect of Hibiscus subdariffa in present study it was consistent with that of [18] that showed an increase in the urine output.

Regarding the parameters that were taken individually, according to ANOVA test: The most significantly effective drug in lowering both the systolic and diastolic blood pressure was furosemide followed by candesartan, atenolol and Hibiscus subdariffa respectively.

This is because the mode of induction of hypertension in this group involves fluid retention and furosemide is most effective in such conditions. These findings are consistent with that of [19].

Concerning the blood flow, candesartan was found to be the most significantly effective drug in increasing blood flow followed by furosemide and Hibiscus subdariffa respectively.

Concerning the urine output furosemide was found to be the most significantly effective drug in increasing urine output followed by Hibiscus subdariffa.

Regarding the blood flow atenolol was found to decrease blood flow significantly due to negative inotropic effect while candesartan was found to increase blood flow significantly. Regarding urine output furosemide was the only drug that significantly increased urine output.

CONCLUSIONS

The above results confirm that candesartan is more effective than atenolol while less effective than furosemide in lowering blood pressure in case of volume loading hypertension. The aqueous extract of Hibiscus subdariffa is effective as antihypertensive agent at the concentration mentioned. Its action involves diuretic and vasodilator effect. While aqueous extracts of Plantago major and Teucrium polium are not effective as antihypertensive drugs at the concentrations mentioned.

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